

REMARKS

A check for the fees for an extension of time accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Claims 17-22, 31, 33, and 35-41 are pending. Claims 18-22, 40 and 41 are allowable. The Final Office Action indicates that claims 35-39 would be allowable if they amended to be dependent on an allowable base claim. Claims 35-39 are not amended herein, however, pending consideration of the remarks below.

Rejection of claims 17, 31 and 33 under 35 U.S.C. §102(b)

The Final Office Action alleges that claims 17, 31 and 33 are anticipated by Nolan *et al.* In particular, it is alleged that the method described by Nolan *et al.* indicates that it is preferable to use chromosomes that are fluorescently labeled that are then detected by fluorimetry. It is alleged that Nolan *et al.* discloses detecting the number of cells that are fluorescent after FACS sorting. It also is alleged that the methods described by Nolan *et al.* include host cells such as fibroblasts and parenchyma stem cells.

Responsive to the Amendment and Response after Final, in which it was argued among other arguments that Nolan *et al.* does not disclose any fluorescent labeling of nucleic acids and subsequent introduction of such nucleic acids into a cell, the Advisory Action counters that the arguments are not persuasive. The Advisory Action urges that Nolan *et al.* states that "It is preferred that the chromosome be fluorescently labeled," and concludes that the reference thus anticipates the claimed methods. The Advisory Action states "Nothing in this sentence indicates that the chromosome must or is labeled after its introduction into the host cell, thus there is no reason to conclude this as a fact." The Advisory Action also alleges that because Nolan *et al.* discloses artificial chromosomes synthesized with AT-rich regions, such AT-segments qualify as a label since they can be detected with dyes. It is further alleged that nothing in the Applicant's specification or claims preclude such AT-rich segments from meeting the limitations of being a "label." Therefore, the Examiner concludes that Nolan *et al.* discloses the instantly claimed methods.

This rejection is respectfully traversed. As discussed below, not only does applicant disagree with the reasons for the rejection, the rejection on its face cannot be improperly set forth under 35 U.S.C. §102(b). As discussed below, the Examiner urges that Nolan *et al.*,

does not state whether or not the nucleic acid is labeled before introducing it into cells. The instant claims specify that the nucleic acid is labeled before introduction into the cells. As acknowledged by the Examiner, Nolan *et al.* does not state that the nucleic acid is labeled before introduction into the cells. Therefore, Nolan *et al.* cannot anticipate any of the rejected claims because *it does not disclose every element as claimed.*

The Claims

Claim 17 is directed to a method for monitoring the delivery of a large nucleic acid molecule into a cell. The method includes the steps of (a) labeling the large nucleic acid molecule; (b) delivering the labeled large nucleic acid molecule into a cell; and (c) detecting the labeled large nucleic acid molecule in the cell by flow cytometry, fluorimetry, cell imaging or fluorescence spectroscopy, as an indication of delivery of nucleic acid molecule into the cells. Dependent claims further specify cell types and an additional step of (d) determining the number of cells containing the label.

Differences between the disclosure of Nolan *et al.* and the rejected claims

Nolan *et al.* describes a method and apparatus for subjecting a cell to a laser light pulse to create a hole in the plasma membrane and introducing a chromosome into the cell. Nolan *et al.* describes the use of FACS to verify chromosome insertion into the cell.

Nolan *et al.* does not disclose delivering *labeled* large nucleic acid molecules of any size into a cell. The statement in Nolan *et al.* that recites, "it is preferred that the chromosome be fluorescently labeled," does not disclose the instantly claimed methods, which specify that the nucleic acids molecules are labeled before they are introduced into a cell. Therefore, this statement does not constitute an anticipatory disclosure.

Further, the only method described in Nolan *et al.* is one in which chromosomes are labeled after they are introduced into a cell. Nolan *et al.* states that one method of verifying insertion of a chromosome into a cell is (1) identification of the inserted chromosome using chromomycin A3 and Hoechst 33258, which are known dyes for staining chromosomes in cells; and (2) FACS sorting of the stained chromosomes. Thus, for example, at page 9, line 25 to page 10, line 6, Nolan *et al.* states:

There are numerous means for determining the successful incorporation of a single chromosome into the cell. It is presently preferred that the verification be made by a FACS machine. Presently, it is preferred that the chromosome be fluorescently labeled. Thus, after insertion of the chromosome, the cell can pass into a recovery chamber where its fluorescent scatter properties are analyzed by the FACS to determine whether one and only one chromosome has been inserted. Current artificial

chromosomes are very AT rich due to the fact that they contain a large percentage of pericentric alpha satellite DNA, which is very AT rich. This type of chromosome is identified and sorted by using chromomycin A3 and Hoechst 33258 stains and dual laser high speed flow cytometry. The AT rich chromosomes carry a specific ratio of the dyes and can be identified in this manner.

The above is the only method involving fluorescent detection that is disclosed by Nolan *et al.* The method involves staining the chromosomes using the known dyes chromomycin A3 and Hoechst 33258 *after* the chromosome is introduced into the cell. Hence, Nolan *et al.* discloses fluorescent labeling *after* the chromosome is delivered into a cell, as a means of verifying that the chromosome has been incorporated into the cell.

Analysis

Nolan *et al.* does not anticipate the instantly claimed methods

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundsciber Corp. v. U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik GmbH v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984).

Each and every element of the instantly claimed methods is not disclosed in Nolan *et al.* Therefore, it is respectfully submitted that the anticipation rejection is improper. The Examiner states in reference to the sentence cited in Nolan *et al.* "it is preferred that the chromosome be fluorescently labeled": "Nothing in this sentence indicates that the chromosome must or is labeled after its introduction into the host cell, thus there is no reason to conclude this as a fact." Even if, as the Examiner appears to imply, this statement encompasses labeling the chromosome before or after its introduction into a cell, such is not the standard for an anticipating disclosure. Disclosure of a genus, and such is not acknowledged in this case, does not anticipate the disclosure of a species.

The Examiner has not pointed to anywhere in Nolan *et al.* that discloses the a method that includes labeling *before* delivery of the nucleic acid molecule to the cell. Hence, even if

it could be argued that Nolan *et al.* discloses the genus of labeling nucleic acid molecules, it does not disclose the species as claimed directed to labeling large nucleic acid molecules *before* delivering them to a cell. As discussed above, the only method described in Nolan *et al.* involves labeling of chromosomes after they are introduced into a cell.

The Examiner additionally alleges that even if the method in Nolan *et al.* only discloses using chromomycin A3 and Hoechst 33258 dyes after introducing a chromosome into a cell, the reference is anticipatory because the chromosomes used by Nolan *et al.* contain AT-rich segments that meet the common definition of "label."

First, it is respectfully submitted that AT rich segments are not labels. Merriam Webster's Collegiate Dictionary (10th edition, 1993) defines label as some matter attached for identification (see page 649 provided herein). In addition, the dictionary defines to label, labeling, labeled, as "to affix a label to," and "to distinguish (an element or atom) by using an isotope distinctive in some manner (as in mass or radioactivity," and "to distinguish (as a compound or cell) by introducing a traceable constituent (as a dye or labeled atom)" (emphasis added; see page 649, provided herein). The dictionary definition is consistent with the use of the terms "label" and "labeling" in the instant application. For example, the instant application exemplifies labeling by the introduction of nucleotide analogs into nucleic acid molecules (see for example, at page 42, lines 4-20 and for example, Example 4 at page 56, lines 21-27). Hence, the application exemplifies the introduction of a traceable constituent into nucleic acid molecules.

In contrast, AT-rich segments as described in Nolan *et al.* are not "introduced" or "affixed" to the artificial chromosomes. They are an integral part of the chromosome. Hence, they do not meet the common definition of "labeling." All DNA sequences can be detected by the nature of their sequence. For example, sequence-specific probes can be used to detect the presence of a complementary sequence of nucleotides in DNA molecule using hybridization. The complementary sequence of nucleotides, however, is not a label because it is not "affixed" or "introduced" into the DNA molecule for the purpose of distinguishing the molecule. Similarly, the detection of AT-rich segments, also is not labeling. AT-rich sequences can be detected by dyes in a similar manner to detecting a DNA sequence by hybridizing a complementary nucleic acid. Nothing is affixed or introduced into the chromosome for purposes of distinguishing the chromosomes, the AT-rich segments are only

sequences of nucleotides inherent in the DNA molecules. Hence, AT-rich segments of a DNA molecule are not labels.

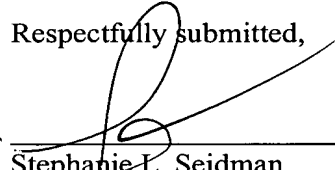
Moreover, the instantly claimed methods specify the step of "labeling large nucleic acid molecules." The term "labeling" is a verb, denoting the action of providing a label to the nucleic acid molecule, not simply detecting a segment that is already present in the nucleic acid molecules. Consistent with the dictionary definitions provided above, labeling denotes the action of affixing or introducing a traceable constituent. Hence, detecting AT-rich segments already present in chromosomes does not affix or introduce a traceable component and thus is not "labeling large nucleic acid molecules."

Therefore, since Nolan *et al.* does not disclose each and every element of the claimed methods, including the steps of labeling large nucleic acid molecules and delivering the labeled large nucleic acid into a cell, the reference does not anticipate the instantly claimed methods. Therefore, Applicant respectfully requests the rejection be withdrawn.

* * *

In view of the above, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,



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Library of Congress Cataloging in Publication Data
Main entry under title:

Merriam-Webster's collegiate dictionary. — 10th ed.

p. cm.

Includes index.

ISBN 0-87779-708-0 (unindexed). — ISBN 0-87779-709-9 (indexed).

— ISBN 0-87779-710-2 (deluxe). — ISBN 0-87779-707-2 (laminated cover).

1. English language—Dictionaries. I. Merriam-Webster, Inc.

PE1628.M36 1993

423—dc20

93-20206

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